Pergamon

Tetrahedron Letters 40 (1999) 3965–3968

TETRAHEDRON
LETTERS

Synthesis of Hirsutene -
An Approach Involving Asymmetric Epoxide Fragmentation

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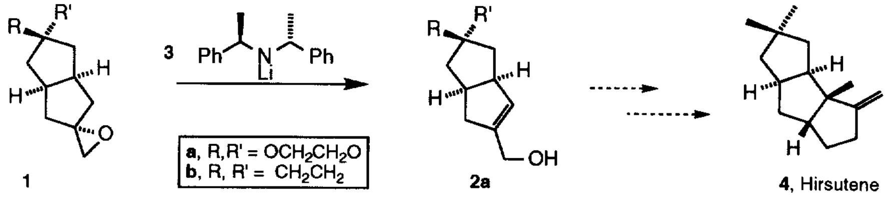
Received 25 February 1999; accepted 22 March 1999

Abstract: A formal synthesis of hirsutene from bicyclo[3.3.0]octanone has been completed. The key step was a lithium amide mediated spiro-epoxide fragmentation reaction. The use of chiral lithium amide bases to induce asymmetry in the epoxide opening step was investigated.

Sometime ago we reported that chiral lithium amide base mediated fragmentation of spiro-epoxide **1a**, using base **3**, provided allylic alcohol **2a** with a high degree of enantioselectivity (80% ee).[1,2] We envisaged that this type of methodology would have potential utility in enantioselective approaches to a range of natural products. Construction of the triquinane ring system of hirsutene **4**,[3] from analogous spiroepoxide **1b**, appeared to be a realistic objective and we now report the fulfilment of this synthetic goal.[4]



Scheme 1

First of all we needed to prepare epoxide fragmentation precursor **1b** from monoketal **5**. Initially, we attempted to introduce the *gem*-dimethyl group as the first synthetic stage (Scheme 2). Wittig reactions on bicyclo[3.3.0]octanones are notoriously temperamental, with enolisation often being a competing process. However, ketone **5** was methylenated in high yield when NaHMDS was used as the base. Alkene **6** was then cyclopropanated efficiently by a modified Simmons-Smith procedure.[5] Reductive opening of the cyclopropane ring, at this stage, was not straightforward. Hydrogenation of **7** at 1 atmosphere with PtO$_2$ in AcOH caused reductive cleavage of the ketal as well as cyclopropane opening, leading to **8**. To avoid such a problem ketone **9** was hydrogenated, but the carbonyl group was reduced preferentially, leading to a mixture of dimethyl and cyclopropyl alcohols **10a/b**. However, when NaOAc was added to the reaction mixture gem-dimethyl compound **11** was obtained cleanly from **9**, albeit in modest yield. Sulfur ylides gave the undesired *endo* spiro-epoxide when reacted with bicyclic ketone **11**, so it was presumed that epoxidation of alkene **12** would provide the required *exo* epoxide. To our surprise, given the efficiency with which we were able to methylenate **5**, we were unable to convert **11** into **12** under any circumstances (for example, Wittig, Peterson and Tebbe's reactions all failed under a variety of conditions).

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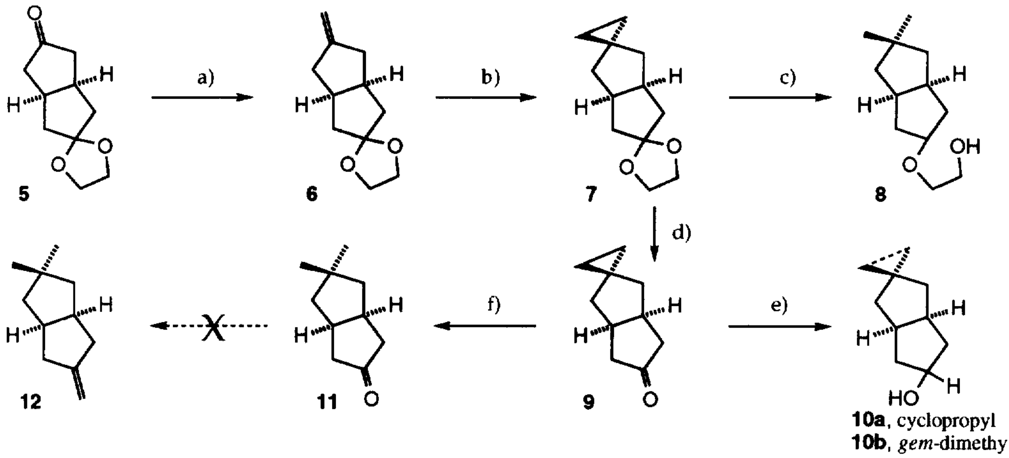
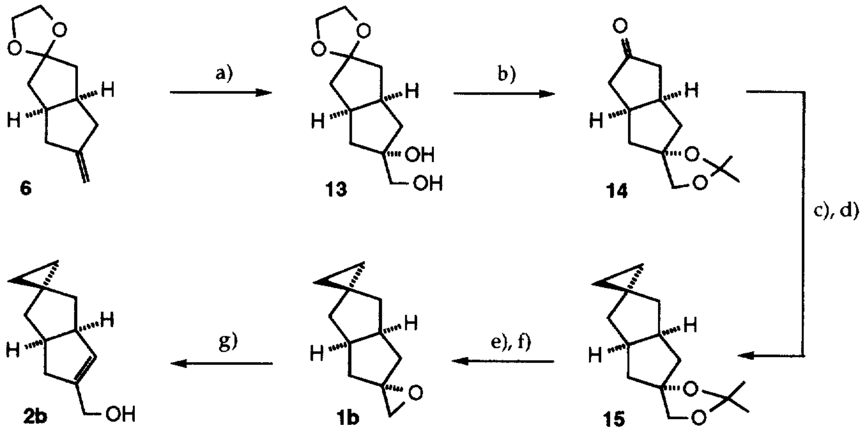
PII: S0040-4039(99)00622-X



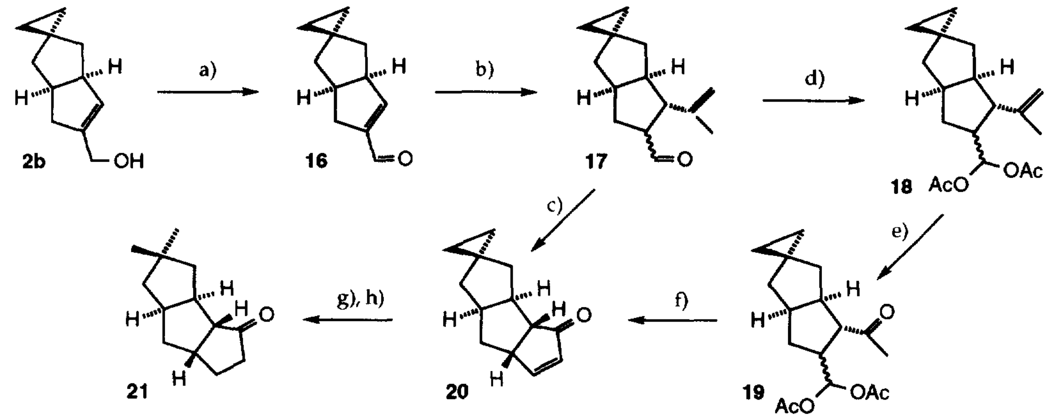
Scheme 2 a) Ph_3PCH_3Br/ NaHMDS/ THF (90%); b) CH_2I_2/ $Zn(Et)_2$/ Et_2O (88%); c) H_2 (1 atm.)/ PtO_2/ AcOH (63%); d) TsOH/ Me_2CO/ H_2O/ reflux (98%); e) H_2 (10 atm.)/ PtO_2/ AcOH (77%); f) H_2 (1 atm.)/ PtO_2/ AcOH/ NaOAc (58%).

Given the difficulties outlined above, we decided to 'turn the problem on its head' and begin by introducing a protected diol group, as a precursor to the spiro-epoxide that was ultimately required. Thus, alkene **6** was dihydroxylated with a catalytic quantity of OsO_4 to provide diol **13** in 83% yield as a 9 : 1 mixture of stereoisomers (*exo* : *endo*). Upon treatment with acidic aqueous acetone, diol **13** was converted into an acetonide and the ketone function was simultaneously deprotected, to provide **14**. The cyclopropane function was then installed in two steps, as before, to give **15** in good overall yield. Finally, the diol acetonide was converted into the required spiro-epoxide by hydrolysis, followed by a one-pot mesylation-epoxide cyclisation process. With an efficient route to *meso* epoxide **1b**, the next synthetic stage was the crucial lithium amide base mediated epoxide fragmentation, to give **2b**. Although this is the asymmetric induction step (see below), the synthetic studies were initially carried out with racemic **2b**, produced in 65% yield using LDA as the base (Scheme 3).



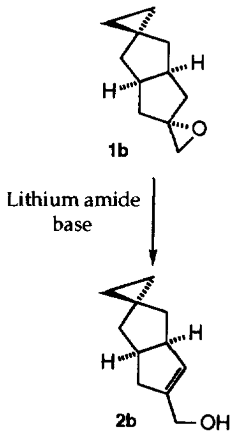
Scheme 3 a) OsO_4/ NMMO/ THF/ H_2O/ tBuOH (83%); b) TsOH/ Me_2CO/ H_2O (3 : 1)/ reflux (79%); c) PPh_3CH_3Br/ NaHMDS/ THF (94%); d) CH_2I_2/ $Zn(Et)_2$/ Et_2O (87%); e) dil. HCl/ THF; f) $MeSO_2Cl$/ Et_3N, then nBuLi/ THF (83%); g) LDA/ THF/ -78°C (65%).

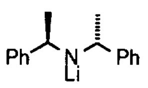
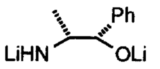
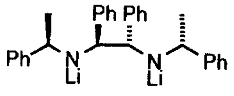
The successful route from alcohol **2b** to hirsutene precursor **21** began with oxidation of the alcohol under Swern conditions to provide **16**. Next, the crucial step of the sequence was a conjugate addition to the α,β-unsaturated aldehyde, a notoriously capricious process. Fortunately we found that a higher order cuprate, formed from isopropenyllithium, reacted smoothly and in good yield under conditions reported by Clive *et al.*[6] The 1,4-addition of the isopropenyl group appeared to be completely stereoselective, but the product **17** was a mixture of stereoisomers at the position adjacent to the aldehyde. Triquinane **20** could be obtained directly from **17** by ozonolysis of the alkene followed by base treatment, but the yield was disappointing, although no other discrete product was isolated. We explored various methods for protecting the aldehyde, including converting it to an alkene, but the most effective route involved the acid stable *bis*-acetate **18**. Ketone **19** was then formed, by *in-situ* dihydroxylation-diol cleavage, and treated with base to provide triquinane enone **20**. Finally, hydrogenation, followed by ketone re-oxidation gave the well known hirsutene precursor **21** with spectroscopic data identical to those reported previously (Scheme 4).[7]



Scheme 4 a) $(COCl)_2$/ DMSO/ Et_3N (72%); b) Isopropenyllithium/ CuI/ TMEDA/ THF (79%); c) i) O_3/ DMS/ CH_2Cl_2/ -78°C; ii) KOH/ THF/ ether/ reflux (10% over 2 steps); d) Ac_2O/ $FeCl_3$ (71%); e) OsO_4/ $NaIO_4$/ dioxane/ H_2O (1 : 1) (40%); f) LiOH/ THF (67%); g) H_2/ PtO_2/ NaOAc/ AcOH (84%); h) PCC/ CH_2Cl_2/NaOAc (77%).

Since acetal epoxide **1a** was opened to give **2a** with high enantioselectivity (80% ee) using chiral lithium amide base **3**, we anticipated that the cyclopropane epoxide **1b** would react in a similar manner. To our surprise **1b** was quite unreactive towards a range of chiral bases that were effective for opening **1a**, and elevated reaction temperatures (~25°C) were required to bring about any reaction. Under such conditions base **3** provided a moderate yield and the small amount of product isolated had low ee. A range of other base types were therefore explored for the reaction (Scheme 5).



Base		Solvent	Yield %	e.e. %
	3	THF Benzene	40 65	23 8
	21	THF	<10%	-
	22	THF	39	9
(-)-Sparteine/^{s}BuLi	23	Ether	50	54

Scheme 5

Bidentate bases **21**, derived from norephedrine,[8] and **22**, derived from α-methylbenzylamine,[9] gave disappointing results in terms of both yields and ee, and the best result so far (54% ee, 50% yield) was achieved using sBuLi/ (-)-sparteine complex. The difference in reactivity of **1a** and **1b** and the fact that **1b** reacts with distinctly lower enantioselectivity is curious. For several types of reaction involving lithium reagents, it has been observed that an oxygen group some distance from the site of reaction can have a significant influence. Indeed, we[1] and others[8,10,11] have reported chiral base epoxide fragmentation processes that are significantly influenced by the nature and position of such groups. It is probable that steric hindrance as well as metal-oxygen co-ordination are important factors and it is possible that, in some cases, there maybe dual mechanistic pathways. A six-membered transition state model has often been envisaged to explain lithium amide driven epoxide fragmentations,[12] but this would not account for the behaviour here, nor the fact that at least two equivalents of base are normally required for these reactions. It is likely that these two phenomena are linked and it is clear that further investigations are required in order to gain a better understanding of these reactions. It may also be that the distinct lack of reactivity of ketone **11** towards Wittig-type reagents (when compared to **5** and **14**) is linked the absence of a remote oxygen functionality. We are continuing to investigate the mechanistic details of lithium amide epoxide fragmentation reactions.

Acknowledgements:

We thank the EPSRC for a studentship (A.M.) and Shell Research for a CASE award (LRB).

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